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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/084,960	HESCHELER, JURGEN	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *February 28, 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/446,717.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application filed February 28, 2002 is a continuation of 09/446,717 filed 04/13/2000, now abandoned, which is a national stage entry of PCT/EP98/03988 with the international filing date of June 30, 1998.

Applicant's amendment filed June 3, 2004, has been received and entered. Claims 42-53 have been canceled. Claims 32-41 are pending.

Election/Restrictions

Applicant's election without traverse of Group I, claims 32–41, in the reply filed on June 3, 2004 is acknowledged (bottom of page 4). Further, it is noted that claims to non-elected inventions have been cancelled.

Claims 32-41 drawn to a cell culture cell-type or development-specific expression of a fluorescent protein are currently under examination.

Priority

It is noted that the specification was amended February 28, 2002 to indicate the priority information. However, if applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Claim Objections

Claim 41 is objected to because of the following informalities:

It appears that pCX-(a-act)GFP-Neo is misspelled and should be set forth as pCX-(α-act)GFP-Neo or pCX-(**alpha**-act)GFP-Neo consistent with promoters discussed in the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 41 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention consists of using pCX-(α-act)GFP-Neo, a specific plasmid construct that has been deposited as DSM 11633. Since the plasmid is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the plasmid is not so obtainable or available, the requirements of 35 U.S.C. 112, regarding "how to make", may be satisfied by a deposit of cell lines. It is noted that Applicant have provided general guidance to the construction of the plasmid, but is unclear if this would necessarily provide pCX-(α-act)GFP-Neo or is what is specifically deposited. In addition, the specication does not provide any indication as to public availability. If the deposits

are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific cell lines have been deposited under the Budapest Treaty and that the cell lines will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

It the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer; and,

(d) a test of viability of the biological material at the time of deposit (see 37 CFR 1.807); and,

(e) the deposit will be replaced if it should ever become inviable.

Claims 32-35, 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". Specifically, claim 32 recites that the promoter used "is substantially inactive in undifferentiated embryonic stem cells", and Applicants amendment does not point to support in the specification for this new embodiment. Upon review of the specification Examiner can not find literal support for this embodiment, and while some of the specific examples of promoters provided in the specification may meet this limitation, it does not appear that this limitation was specifically contemplated. Importantly, there is no teaching nor discussion on what would be considered "substantially inactive" to determine the metes and bounds of this embodiment relative to the claimed invention.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 32-35, 39 and 40 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as

filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32, 33, 35, 36, 39 and 40 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Zernicka-Goetz *et al.*

Claims 15-18, 20, 22-24, 26-28 are drawn to cell cultures of embryonic stem cells stably transfected with a DNA construct comprising a DNA sequence coding for a non-cell-damaging fluorescent protein operably linked to a cell-/development-dependent promoter integrated in the native DNA. . Zernicka-Goetz *et al.* teach a stable mouse ES cell line that expressed MmGFP (summarized in the abstract). The transgene construct which contains the GFP gene operably linked to the cdc2 promoter for expression in proliferating cells, was electorporated into ES cells and allowed to intergrate into the genome of the ES cell line (page 1134; first and last paragraph of column 2). To induce cell differentiation, cells were aggregated in culture in order to form

embryonal bodies (page 1134; first paragraph). Finally, chimeric transgenic mice were produced using the ES cell lines by injecting the cells into a blastocyst, implanting the chimeric embryo into a surrogate mother and allowing the embryo to come to term, wherein examination of the fibroblasts showed expression of GFP (top of page 1134 and page 1136; figure 4). Thus the claims are anticipated by Zernicka-Goetz *et al.*

Applicants argue that the cdc2 promoter taught in Zernicka-Goetz *et al.* is not a "cell- and/or development dependent" promoter. Applicants argue that the cdc2 promoter is active in all proliferating cells and only after differentiation of the ES cell can one detect a change in expression of the cdc2 promoter (see preliminary arguments presented in Applicant's amendment, page 6). Further, Applicant points out in their arguments that after differentiation of the ES cell one can one detect a change in expression of the cdc2 promoter (see Applicant's amendment, page 7). As noted previously, the specification broadly defines the term "cell- and/or development-dependent promoter" as a promoter which displays activity in a particular cell type or a stage of cellular development (specification, page 4), and while the Examiner would agree that the cdc2 promoter is not one of the promoters listed as examples in the specification, in view of the broad definition provided by the specification of a "cell- and/or development-dependent promoter", a cdc2 promoter could be considered indicative of terminal differentiation or would be expressed in cell types which are actively proliferating, and thus anticipate this embodiment of the claim. As noted in previous arguments and taught by Zernicka-Goetz *et al.* the cdc2 promoter activity decreases after differentiation and in cells which are not proliferating.

It is noted that Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32, 33, 35-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zernicka-Goetz *et al.* in view of Ikawa *et al.* and in further view of Wobus *et al.*, Sartorelli *et al.* and Chen *et al.*

Claims 32, 33, 35, 36, 39 and 40 are summarized above. Claims 37 and 38 encompasses the use of the Nkx-2.5, human alpha-actin or MLC-2V promoters As discussed above, Zernicka-Goetz *et al.* clearly anticipate claims 32-36, 39 and 40 but, they do not teach specifically use Nkx-2.5, human alpha-actin or MLC-2V promoters. Ikawa *et al.* teach the pCX-GFP vector construct with the beta-actin and CD4 promoters operably linked to GFP for use as a marker in transgenic studies. Wobus *et al.* teach the MLC-2v promoter which is expressed cardiomyocytes and can be used in toxicological studies, Sartorelli *et al.* teach the human cardiac alpha-actin promoter, and Chen *et al.* teach the nkx-2.5 promoter which is the murine cardiac-specific homeodomain gene. Each, Wobus *et al.*, Sartorelli *et al.* and Chen *et al.*, use the promoters in

reporter vector constructs to study the effects on promoter expression, and in particular, Wobus *et al.* teach to use their vector construct in ES cells induced to develop into cardiomyocytes to study pharmocological and toxicological effects on cardiomyocytes. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to create a pCX-GFP reporter vector construct as described by Ikawa *et al.* which contain the cardiac specific promoters described by Wobus *et al.*, Sartorelli *et al.* and Chen *et al.* One having ordinary skill in the art would have been motivated to substitute the beta actin or CD4 promoter in the pCX-GFP vector used by Ikawa *et al.* with the promoters described by Wobus *et al.*, Sartorelli *et al.* and Chen *et al.* to more easily study the regulatory sequences of the promoter in developmental, pharmacological and toxicological studies of cardiomyocytes derived from ES cell lines. There would have been a reasonable expectation of success given the results of Ikawa *et al.* to substitute the promoters of Wobus *et al.*, Sartorelli *et al.* or Chen *et al.* into the pCX-GFP vector for use in ES cells. Further, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the pCX-GFp vectors in the methods of described in Zernicka-Goetz *et al.* to create stably transfect ES cell lines for following cell fate and for the creation of transgenic mice. One having ordinary skill in the art would have been motivated to substitute the pCX-GFP vector used by Ikawa *et al.* with the promoters described by Wobus *et al.*, Sartorelli *et al.* and Chen *et al.* to more easily study the regulatory sequences of the promoter in developmental, pharmacological and toxicological studies of cardiomyocytes in stably transfected ES cell lines. There would have been a reasonable expectation of success to substitute the pCX-GFP vector containing the cardiac

specific promoters in the methods taught by Zernicka-Goetz *et al.* given the results of Ikawa *et al.* in the use of the vector for transgenic work.

Applicants argue that Zernicka-Goetz *et al.* is not enabling, pointing out that one may expect that small fluorescent proteins like GFP may not be retained within a single cell. This is unconvincing because Zernicka-Goetz *et al.* do not show this phenomena, and Applicants do not provide any supporting evidence to support this assertion. It is well known in the art that many molecules, in particular proteins, no matter the size, do not freely diffuse through the cell membrane. In addition, Examiner would agree that GFP when highly expressed may can kill the cell, however, the results of Zernicka-Goetz *et al.* do not support Applicants assertion. Further, as pointed out in Huang *et al.* (supplementary reference cited by Applicant) this general problem was recognized in the art with respect to GFP and other proteins used as marker/reporter genes. At the time of filing, it was generally known that it is not the protein *per se* which is the problem, rather it is the level of expression of the protein which cause the cell death. However, in addition to the examples of Zernicka-Goetz *et al.* and Ikawa *et al.*, there are numerous examples of transgenic mice expressing reporter genes present in the art, which fairly suggest that the use of GFP in transgenic animals, as well is cell culture is fully enabled. Finally, Applicants argue that Zernicka-Goetz *et al.* do not teach the importance of expression fluorescent proteins in differentiating cells or the potential toxicity to the cells. These arguments are unconvincing because Zernicka-Goetz *et al.* is relied upon for what they teach, not what they do not teach. The analysis of promoter constructs with the use of a reporter gene is routine in the art. The artisan is well aware of the possible shortcomings of the use of any reporter gene, including GFP. Zernicka-Goetz *et al.* teach a stable mouse ES cell line that expresses MmGFP. Cells were

aggregated in culture in order to form embryonal bodies and chimeric transgenic mice were produced using the ES cell lines by injecting the ES cells into a blastocyst, implanting the chimeric embryo into a surrogate mother and allowing the embryo to come to term, wherein examination of the fibroblasts showed expression of GFP. Finally, Zernicka-Goetz *et al.* suggest that these marked cells will be important both for identifying cell migration and cell lineage analyses (page 1136, last paragraph).

Claims 32-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zernicka-Goetz *et al.*, Ikawa *et al.*, Wobus *et al.*, Sartorelli *et al.* and Chen *et al.* in view of Maltsev *et al.* (Circulation Research, 75:233-244) or Rohwedel *et al.* (Developmental Biology 164:87-101).

The teachings of Zernicka-Goetz *et al.*, Ikawa *et al.*, Wobus *et al.*, Sartorelli *et al.* and Chen *et al.* are discussed above, however none of the references teaches to use the hanging drop technique to obtain aggregate embryoid bodies. Maltsev *et al.* and Rohwedel *et* al. teach the production of embryoid bodies by the hanging drop technique. Maltsev *et al.* and Rohwedel *et al.* provide the specific culture conditions to obtain differentiated muscle and cardiac specific cell types by this method (summarized in figure 1 in both references), and at the time of filing is was routine to develop embryoid bodies by various methods for the analysis of developmentally regulated gene expression. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to create a pCX-GFP reporter vector construct as described by Ikawa *et al.* which contain the cardiac specific promoters described by Wobus *et al.*, Sartorelli *et al.* and Chen *et al.* One having ordinary skill in the art would have been motivated to substitute the beta actin or CD4 promoter in the pCX-GFP vector used by

Ikawa *et al.* with the promoters described by Wobus *et al.*, Sartorelli *et al.* and Chen *et al.* to more easily study the regulatory sequences of the promoter in developmental, pharmacological and toxicological studies of cardiomyocytes derived from ES cell lines. Further, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the appropriate culturing conditions to obtain the differentiated cell of choice. One having ordinary skill in the art would have been motivated to use the hanging drop technique to derive embroid bodies because it provides a excellent in vitro system to study the process of muscle and cardiac development as described in Maltsev *et al.* and Rohwedel *et al.* There would have been a reasonable expectation of success to substitute the hanging drop method for other culturing conditions such as those taught in Zernicka-Goetz *et al.* given the successful results of Maltsev *et al.* and Rohwedel *et al.*

Conclusion

No claim is allowed. Claim 41 is free of the art of record because the art fails to teach the specific vector deposited as DSM11633, however the claim is subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

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